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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,663	08/05/2003	Sidney T. Smith	TR-5934	6356

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EXAMINER	
BOWERS, NATHAN ANDREW	
ART UNIT	PAPER NUMBER
1797	
MAIL DATE	DELIVERY MODE
06/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,663	SMITH ET AL.	
	Examiner	Art Unit	
	NATHAN A. BOWERS	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,19-21 and 23-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,19-21 and 23-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 3-11, 19-21, 23-34 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of either Toner (US 6759245) or Turner (US 5912177), and further in view of Codner (US 5686304).

With respect to claims 1 and 48, Smith discloses a closed cell culture container (Figure 2:20) comprising a first flexible sidewall (Figure 2:22) connected to a portion of an opposing second flexible sidewall (Figure 2:24) along a peripheral seal to define a containment area (Figure 2:26). This is disclosed in column 6, lines 12-33. Column 2, lines 24-31 and column 3, line 59 to column 4, line 46 teach that the first and second sidewalls are constructed from flexible polymeric materials that permit cellular respiration. Column 5, lines 39-45 indicate that the sidewalls are constructed from ethylene vinyl acetate. A polystyrene layer (Figure 2:12) is provided to promote cell adhesion to the inside surface of the culture container. Smith, however, does not expressly state that a fibrin matrix layer is positioned on a portion of the interior surface of the first or second sidewalls of the cell culture container.

Toner discloses a cell culturing device (Figure 1) that includes a chamber divided by a gas permeable, liquid impermeable polymeric membrane (Figure 2:30). Cells (Figure 2:40) are seeded upon the membrane, and gases from an oxygenated liquid stream (Figure 2:20) are allowed to diffuse through the membrane in order to contact the cells. This is disclosed in column 3, lines 1-25 and column 7, line 10 to column 8, line 19. Column 9, lines 8-42 indicate that the membrane may be constructed from a variety of polymer compounds arranged in a single or multi-layered assembly. Column 11, lines 27-56 teach that the membrane (Figure 1:30) is coated with a fibrin matrix layer (Figure 1:41) to increase cell adhesion.

Turner discloses a polymer bag that forms a closed container for holding a cell culture. Column 3, lines 47-65 state that the bag is permeable to gases vital for cellular metabolism. Column 2, lines 43-50 indicate that a fibrin matrix is immobilized upon the inner walls of the bag in order to facilitate the adhesion of cells.

Smith, Toner and Turner are analogous art because they are from the same field of endeavor regarding cell culture containers.

At the time of the invention, it would have been obvious to include a fibrin matrix layer positioned on the interior surface of the polystyrene layer disclosed by Smith. In column 6, line 65 to column 7, line 19, Smith teaches that it is desirable to provide a culture vessel which includes sidewalls that are capable of accommodating adherent dependent cells. Toner and Turner each teach that fibrin, when applied to a polymer substrate, will enhance cell immobilization to the polymer substrate. In this way, Smith's invention would be improved through the addition of a fibrin matrix layer because the fibrin matrix would allow the cell culture container to better accommodate a wider range of adherent dependent cell types.

The combination of Smith and Toner/Turner still differs from Applicant's claimed invention because it is not entirely clear if the inner surface of Smith's container comprises an ethylene vinyl acetate copolymer. The Figures predominantly indicate that the inner surface of the container is covered by a polystyrene layer (Figure 8:28) as opposed to an ethylene vinyl acetate copolymer layer (Figure 8:24).

Codner discloses a cell culture apparatus. In column 6, line 53 to column 7, line 5, Codner teaches that the walls defining the apparatus comprise an inner surface formed from an ethylene vinyl acetate copolymer.

Smith, Toner, Turner and Codner are analogous art because they are from the same field of endeavor regarding cell culture bags.

At the time of the invention, it would have been obvious to form the inner surfaces of Smith's container from areas comprising polystyrene and fibrin materials as well as areas comprising ethylene vinyl acetate copolymers. As previously described above, polystyrene and fibrin are beneficial because they foster the growth of adherent cells. However, Smith teaches in column 7, lines 35-36 that ethylene vinyl acetate is more suitable for the culture of non-adherent cells, and, as evidenced by Codner, the use of ethylene vinyl acetate copolymers is well known in the art. It would have been obvious to ensure that some areas of Smith's inner surface are covered by fibrin and polystyrene to encourage the growth of adherent cells, and it would have been obvious to ensure that other areas of Smith's inner surface are covered by ethylene vinyl acetate copolymers to promote the culture of non-adherent cells.

With respect to claims 3 and 4, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith teaches in column 4, lines 11-46 that the gas permeable material is either EVA, polyolefin, polyamide or styrene. The polymeric material of the first sidewall is a styrene and hydrocarbon multi-component polymer blend.

With respect to claims 5-11, 49 and 50, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith teaches that the gas permeable material is either a monolayer or a multilayer structure. Monolayer cell culture containers are well known in the art, and Figures 1 and 4 illustrate multilayer embodiments. A polystyrene layer (Figure 4:12) and a skin layer (Figure 4:18) are provided in addition to the substrate layer (Figure 4:14). Column 5, lines 7-18 teach that the skin layer and substrate layer are formed on the outer surface of the polystyrene layer, so that the inner surface of the polystyrene layer forms the interior surface of the culture chamber. The skin layer is formed from polyethylene copolymers and polypropylene copolymers. Column 4, lines 11-46 indicate that substrate layer is anywhere from 0-40% ethylene vinyl acetate copolymer. It is an intrinsic feature of the invention that the composition of the substrate and polystyrene layers can be manipulated in order to achieve any desired polymer distribution.

The claimed weight ratios are simply result effective variables. In the absence of new or unexpected results, it would have been obvious to optimize the composition of the substrate and skin layers. This optimization could simply be accomplished by producing different compositions and testing their ability to be used in cell culturing. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

With respect to claims 19-21, 23-26 and 51-53, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 2, lines 24-31 that the polystyrene layer (1st layer) has a thickness within the range of 0.0001 inches to 0.001 inches. Column 4, lines 47-56 indicate that the substrate layer (2nd layer) has a

thickness of 0.004 inches to 0.025 inches. Column 4, lines 11-46 teach that the second layer is a multi-component polymer blend that includes styrene and hydrocarbon copolymer. Figure 2 indicates that the gas permeable EVA material is used in the construction of both the first and second sidewalls. The nature of the invention regarding copolymer content and layer thickness has already been described.

With respect to claims 27-32, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 2, lines 39-51 that the culture container has a oxygen permeability of 9-15 Barrers, a carbon dioxide permeability of 40-80 Barrers, a nitrogen permeability of 10-100 Barrers and a water vapor transmission rate of less than 20 (g mil/100 in^2/day). Column 5, line 49 to column 6, line 8 indicates that the first and second sidewalls have a flexural modulus of 10,000-30,000 psi, and that the sidewalls are optically clear. The container is radiation sterilizable. Column 7, lines 39-44 indicate that at least one port (Figure 9:40) provides access to the containment area.

With respect to claims 34 and 35, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 6, line 66 to column 7, line 19 that the inside surfaces of the culture container can be modified in order to determine to what areas cells are allowed to adhere. Accordingly, it would have been obvious to apply the fibrin matrix disclosed by Toner to any part of the container surface that is desired to promote cell adhesion. This intrinsically could pertain to the entire inner surface of the container, or just specific regions of the inner surface. If the culture container is intended to

facilitate the growth of adherent cell types, then it would be obvious to apply the fibrin matrix to the entire sidewall interior surface. If the culture container is intended to facilitate the growth of adherent and non-adherent cell types, then it would be obvious to apply to fibrin matrix to just a part of the sidewall interior surface.

2) Claims 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of Toner (US 6759245)/Turner (US 5912177) and Codner (US 5686304) as applied to claim 1, and further in view of Delmotte (US 5989215).

With respect to claims 35-37, Smith, Toner/Turner and Codner disclose the invention set forth in the 35 U.S.C. 103 rejections above, however do not expressly disclose the nature of the fibrin matrix.

Delmotte discloses a method for forming a fibrin matrix that includes delivering a first solution of fibrinogen and factor XIII and a second solution of thrombin and calcium to a desired surface. This is disclosed in column 3, lines 31-44 and column 8, lines 3-15. In column 12, line 34 to column 13, line 20, Delmotte states that the amount of thrombin added to the fibrinogen solution is directly related to the pore size of the fibrin matrix product. Thrombin can be added in varying amounts in order to create a fibrin network characterized by pore diameters anywhere between 0.2-4 microns.

Smith, Toner/Turner, Codner and Delmotte are analogous art because they are from the same field of endeavor regarding cell culture systems.

At the time of the invention, it would have been obvious to form a fibrin matrix within the cell culture container disclosed by Smith and Toner by mixing a solution of fibrinogen with a

solution of thrombin. In column 4, line 57 to column 5, line 16, Delmotte states that by separating fibrinogen and thrombin into two separate solutions, one is able to more easily manipulate the concentrations of fibrinogen and thrombin to effect change in the characteristics of the resultant fibrin film. In this way, the concentration of thrombin can be readily changed in order to create a fibrin matrix with a desired pore size.

With respect to claims 38-46, Smith, Toner/Turner, Codner and Delmotte disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In column 7, lines 29-32, Delmotte teaches that the components of the fibrinogen and thrombin are derived from human plasma. It would have been obvious to utilize recombinant components of fibrinogen and thrombin, as well. When the fibrin matrix is used in a bioreactor and not for treating a human being, it is less important to use fibrinogen and thrombin attained from human blood plasma. Techniques for creating recombinant biomolecules are well known in the art.

With respect to claim 47, Smith, Toner/Turner, Codner and Delmotte disclose the apparatus set forth in claim 37 as set forth in the 35 U.S.C. 103 rejection above. In addition, Delmotte discloses in column 8, lines 3-29 that fibrin is made from a first solution containing 10-40 IU/ml of fibrinogen and factor XIII, and a second solution containing 3-10,000 IU/ml of thrombin and 45 micromoles/ml of calcium. Column 15, lines 1-15 disclose a method in which the fibrinogen and thrombin solutions are repeatedly applied to a surface in 0.3 ml increments. Column 18, lines 51-63 disclose a method in which 3.5 ml of the fibrinogen and thrombin

solutions are mixed to form a fibrin matrix. The fibrinogen and thrombin solutions are incubated, and the formed fibrin matrix has a pore size of anywhere between 0.2-4 microns.

Response to Arguments

Applicant's arguments filed 26 February 2008 with regard to the 35 U.S.C. 103 rejections involving the combination of Smith with either Toner or Turner and Codner have been fully considered but they are not persuasive.

Applicant's principle arguments are

(a) Smith is directed to a flexible, gas-permeable container, whereas Toner is directed to a rigid and impermeable cartridge. The suggested combination would change the principle of operation of the Smith apparatus.

In response to Applicant's arguments, please consider the following comments.

The previous Office Actions fully address this issue. The addition of a fibrin layer to the interior walls of Smith would not serve to substantially change the operation of the Smith culture bag.

(b) Smith does not disclose using ethylene vinyl acetate copolymer as any part of the inner cell growth surface layer. Moreover, Smith explicitly teaches away from an interior surface comprising an ethylene vinyl acetate copolymer by stating that the decay of the charge on EVA will render the container ineffective for growing adherent cells.

In response to Applicant's arguments, please consider the following comments.

It is agreed that Smith indicates that EVA is undesirable for the culture of adherent cells. However, Smith describes an embodiment in column 6, line 65 to column 7, line 20 and in Figure 7 indicating that at least one interior surface of the cell bag is constructed from materials compatible with non-adherent cells. EVA, as evidenced by Codner, is known in the art as a material capable of facilitating the growth of non-adherent cells. Accordingly, it would have been obvious to ensure that some areas of Smith's inner surface are covered by fibrin and polystyrene to encourage the growth of adherent cells, and it would have been obvious to ensure that other areas of Smith's inner surface are covered by ethylene vinyl acetate copolymers to promote the culture of non-adherent cells. The addition of fibrin and EVA to Smith's hybrid cell culture bag (Figure 7) would enhance the growth of both adherent and non-adherent cells.

(c) Codner fails to disclose the use of fibrin for growing cells anywhere in his disclosure.

In response to Applicant's arguments, please consider the following comments.

As noted above, Codner is not relied upon for teachings regarding the use of fibrin. The Toner and Turner references each describe that it is beneficial to provide a fibrin layer for the culture of adherent cells. Codner is merely relied upon as evidence that it is well established in the art to provide cell culture bags constructed from EVA materials.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/William H. Beisner/
Primary Examiner, Art Unit 1797

/Nathan A Bowers/
Examiner, Art Unit 1797